PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 June 2001 (21.06.01)	
International application No. PCT/EP00/08995	**Applicant's or agent's file reference** 80270/WO
International filing date (day/month/year) 14 September 2000 (14.09.00)	**Priority date** (day/month/year) 07 October 1999 (07.10.99)
Applicant BERGER, Alvin et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   11 April 2001 (11.04.01)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

STRAUS, Alexander
BECKER, KURIG, STRAUS
Bavariastrasse 7
D-80336 München
ALLEMAGNE

BECKER KURIG STRAUS
BAVARIASTRASSE 7 · 80336 MÜNCHEN
10. Dez. 2001
WV: ..... / LF: .....

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	07.12.2001
Applicant's or agent's file reference: 80270/WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08995	14/09/2000	07/10/1999

Applicant
SOCIETE DES PRODUITS NESTLE S.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Tantum, P Tel.+49 89 2399-8143

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
80270/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08995	14/09/2000	07/10/1999

International Patent Classification (IPC) or national classification and IPC
A23L1/30

Applicant
SOCIETE DES PRODUITS NESTLE S.A.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/04/2001	07.12.2001

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Couzy, F

Telephone No. +49 89 2399 7503

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/08995

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, pages:

1-16	as originally filed				

Claims, No.:

1-16	as received on	10/10/2001	with letter of	10/10/2001	

Drawings, No.:

1-7	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 16 (IA).

because:

☒ the said international application, or the said claims Nos. 16 (Rule 67.1.iv) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrativ Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-13, 15, 16

	No:	Claims	14
Inventive step (IS)	Yes:	Claims	1-13, 15, 16
	No:	Claims	14
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT). This claim was however examined for novelty and inventive step (Articles 33 (2) and (3) PCT).

Re Item V

Reasoned statement under Art. 35.2 with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: WO 96 40106 A (MARTEK BIOSCIENCES CORP ;KYLE DAVID J (US); LINSERT HENRY JR (US)) 19 December 1996 (1996-12-19)

D2: US-A-5 874 459 (HILL WILLIAM ADAM ET AL) 23 February 1999 (1999-02-23) cited in the application

D3: WO 94 12466 A (YISSUM RES DEV CO ;DEVANE WILLIAM A (US); MECHOULAM RAPHAEL (IL);) 9 June 1994 (1994-06-09)

D4: WO 96 37200 A (SCOTIA HOLDINGS PLC ;STORDY BARBARA JACQUELINE (GB)) 28 November 1996 (1996-11-28)

D5: EP-A-0 733 360 (SCOTIA HOLDINGS PLC) 25 September 1996 (1996-09-25)

D6: EP-A-0 409 559 (EFAMOL HOLDINGS) 23 January 1991 (1991-01-23)

D7: WO 94 28913 A (MARTEK BIOSCIENCES CORP) 22 December 1994 (1994-12-22)

D8: EP-A-0 490 561 (EFAMOL HOLDINGS) 17 June 1992 (1992-06-17)

V.1 **Novelty (Art. 33 (2) PCT) and inventive step (Art. 33 (3) PCT)**

V.1.a None of the prior art documents discloses nutritional or therapeutic compositions comprising the precursors mentioned in independent claim 1, which are **derivatives** of long chain polyunsaturated fatty acids and are metabolised in the body to compounds

having anandamide activity. Nutritional or therapeutic compositions comprising these fatty acids, but n t their derivatives, are known. For instance, D1 discloses nutritional or therapeutic compositions for oral administration which comprise docosahexaenoic and/or arachidonic acid (p.28 li.3-8, p.29 li.11-23) and which are used as medicaments (claims 61, 1, 28-29). Thus, the compositions of independent claim 1 and of claims 2-13 dependent thereof are new in the sense of Article 33 (2) PCT.

The claimed compositions allow to incorporate precursors of compounds having an anandamide activity in the N-acyl ethanolamines of the brain, as demonstrated by the results presented in the Demand (see e.g. Tables 3-4 on p.12). This might be relevant for the treatment and prevention of diseases and disorders having a neurological component (see p.2 li.26-p.3 li.1 and claim 16 of the Demand). These effects are **not** suggested by the available prior art, which teaches that pure fatty acids or their ethanolamide derivatives may impact neurologic conditions and the anadamide pathway (see e.g. D3). The ethanolamide derivatives are not among those claimed in the present invention. Thus the claimed compositions comprise alternative compounds and involve an inventive step in the sense of Art. 33 (3) PCT.

V.1.b The compounds arachidonic and docosahexaenoic acids mentioned in D1 are precursors of compounds having anandamide activity. Thus, this desired characteristic is implicitly comprised in the disclosure of D1, where such compounds are identified and purified, even if the intended use mentioned in D1 does not mention the anandamide activity. For that reason, the subject-matter of independent claim 15 is not new.

V.1.c Since the compositions of claims 1-13 meet the requirements of the PCT as regard novelty and inventive step, this is also true for the subject-matter of independent claims 15-16 relating to the use of these compositions in the manufacture of a nutritional or therapeutic composition, and a method of treatment which comprise administering these.

Re Item VII
Certain defects in the international application

VII.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D4-D8 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII
Certain observations on the international application

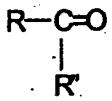
VIII.1 The vague wordings "but are not limited to" on p.2 li.15 and "It should be..." on p.16 li.6-11 introduces lack of clarity of the subject-matter to which the claims refer (Art. 6 PCT). Typo mistakes for the words "effects", "MAG" are apparent on p.2 li.11-13 (Art. 6 PCT).

VIII.2 The vague word "lower" introduce lack of clarity in the subject-matter of dependent claim 2 (Art. 6 PCT).

10/089658
Amended claims 1013 Rec'd PCT/PTO 28 MAR 2002

1. A nutritional or therapeutic composition for oral administration, which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, having a methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, or a seleno-moiety.

2. A composition according to claim 1 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from –H, lower alkyl, -OH, NH_3, and $NHCH_2CH_2OH$, or an acid addition salt or complex thereof.

3. A composition according to claim 2 wherein the precursor comprises a molecule having a plurality of formula X.

4. A composition according to claim 2 or 3 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone, in a sterochemical configuration selected from: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; *sn*-3.

5. A composition according to any preceding claim wherein the precursor comprises a fatty acid selected from the group which comprises arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (20:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) or the Mead acid (20:3n-9).

6. A composition according to any preceding claim wherein the precursor comprises arachidonate (20:4n-6 AA).

7. A composition according to any preceding claim which comprises an inhibitor of an anandamide inactivating enzyme (amidase).

8. A composition according to claim 7 wherein the inhibitor is selected from the group which comprises oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, 2-linoleylglycerol.

9. A composition according to claim 7 or 8 wherein the inhibitor is palmitate or palmitoylethanolamide.

10. A composition according to any preceding claim which comprises a triacylglycerol having palmitate and arachidonate attached to its backbone wherein arachidonate is at the *sn*-1 and *sn*- 2 positions.

11. A composition according to any preceding claim which comprises a compound which reacts with a CB receptor.

12. A composition according to any preceding claim which comprises a steroidal or

non-steroidal anti-inflammatory drug (NSAID).

13. A composition according to any preceding claim which comprises a physiologically acceptable carrier, diluent or adjuvant.

14. A method of production of a nutritional or therapeutic composition for oral administration which comprises the steps of identifying, purifying or synthesising a naturally occurring precursor that is metabolised to a compound having anandamide activity.

15. Use of a composition according to any one of claims 1 to ~~14~~ 13 in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausia, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception.

16. A method of treatment of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausia, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering an effective amount of a composition according to any one of claims 1 to ~~14~~ 13.

PATENT COOPERATION TREATY

REC'D 11 DEC 2001
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
80270/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08995	14/09/2000	07/10/1999
International Patent Classification (IPC) or national classification and IPC A23L1/30		
Applicant SOCIETE DES PRODUITS NESTLE S.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/04/2001	07.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Couzy, F Telephone No. +49 89 2399 7503

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/08995

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-16	as originally filed

Claims, No.:

1-16	as received on	10/10/2001	with letter of	10/10/2001

Drawings, No.:

1-7	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 16 (IA).

because:

☒ the said international application, or the said claims Nos. 16 (Rule 67.1.iv) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-13, 15, 16

	No:	Claims	14
Inventive step (IS)	Yes:	Claims	1-13, 15, 16
	No:	Claims	14
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT). This claim was however examined for novelty and inventive step (Articles 33 (2) and (3) PCT).

Re Item V

Reasoned statement under Art. 35.2 with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: WO 96 40106 A (MARTEK BIOSCIENCES CORP ;KYLE DAVID J (US); LINSERT HENRY JR (US)) 19 December 1996 (1996-12-19)

D2: US-A-5 874 459 (HILL WILLIAM ADAM ET AL) 23 February 1999 (1999-02-23) cited in the application

D3: WO 94 12466 A (YISSUM RES DEV CO ;DEVANE WILLIAM A (US); MECHOULAM RAPHAEL (IL);) 9 June 1994 (1994-06-09)

D4: WO 96 37200 A (SCOTIA HOLDINGS PLC ;STORDY BARBARA JACQUELINE (GB)) 28 November 1996 (1996-11-28)

D5: EP-A-0 733 360 (SCOTIA HOLDINGS PLC) 25 September 1996 (1996-09-25)

D6: EP-A-0 409 559 (EFAMOL HOLDINGS) 23 January 1991 (1991-01-23)

D7: WO 94 28913 A (MARTEK BIOSCIENCES CORP) 22 December 1994 (1994-12-22)

D8: EP-A-0 490 561 (EFAMOL HOLDINGS) 17 June 1992 (1992-06-17)

V.1 **Novelty (Art. 33 (2) PCT) and inventive step (Art. 33 (3) PCT)**

V.1.a None of the prior art documents discloses nutritional or therapeutic compositions comprising the precursors mentioned in independent claim 1, which are **derivatives** of long chain polyunsaturated fatty acids and are metabolised in the body to compounds

having anandamide activity. Nutritional or therapeutic compositions comprising these fatty acids, but **not** their derivatives, are known. For instance, D1 discloses nutritional or therapeutic compositions for oral administration which comprise docosahexaenoic and/or arachidonic acid (p.28 li.3-8, p.29 li.11-23) and which are used as medicaments (claims 61, 1, 28-29). Thus, the compositions of independent claim 1 and of claims 2-13 dependent thereof are new in the sense of Article 33 (2) PCT.

The claimed compositions allow to incorporate precursors of compounds having an anandamide activity in the N-acyl ethanolamines of the brain, as demonstrated by the results presented in the Demand (see e.g. Tables 3-4 on p.12). This might be relevant for the treatment and prevention of diseases and disorders having a neurological component (see p.2 li.26-p.3 li.1 and claim 16 of the Demand). These effects are **not** suggested by the available prior art, which teaches that pure fatty acids or their ethanolamide derivatives may impact neurologic conditions and the anadamide pathway (see e.g. D3). The ethanolamide derivatives are not among those claimed in the present invention. Thus the claimed compositions comprise alternative compounds and involve an inventive step in the sense of Art. 33 (3) PCT.

V.1.b The compounds arachidonic and docosahexaenoic acids mentioned in D1 are precursors of compounds having anandamide activity. Thus, this desired characteristic is implicitly comprised in the disclosure of D1, where such compounds are identified and purified, even if the intended use mentioned in D1 does not mention the anandamide activity. For that reason, the subject-matter of independent claim 15 is not new.

V.1.c Since the compositions of claims 1-13 meet the requirements of the PCT as regard novelty and inventive step, this is also true for the subject-matter of independent claims 15-16 relating to the use of these compositions in the manufacture of a nutritional or therapeutic composition, and a method of treatment which comprise administering these.

Re Item VII

Certain defects in the international application

VII.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D4-D8 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

VIII.1 The vague wordings "but are not limited to" on p.2 li.15 and "It should be..." on p.16 li.6-11 introduces lack of clarity of the subject-matter to which the claims refer (Art. 6 PCT). Typo mistakes for the words "effects", "MAG" are apparent on p.2 li.11-13 (Art. 6 PCT).

VIII.2 The vague word "lower" introduce lack of clarity in the subject-matter of dependent claim 2 (Art. 6 PCT).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/24645 A1

(51) International Patent Classification[7]: A23L 1/30, A61K 31/20

(21) International Application Number: PCT/EP00/08995

(22) International Filing Date:
14 September 2000 (14.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9923738.0 7 October 1999 (07.10.1999) GB

(71) Applicant *(for all designated States except US)*: **SOCIETE DES PRODUITS NESTLE S.A.** [CH/CH]; P.O. Box 353, CH-1800 Vevey (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BERGER, Alvin** [US/CH]; Nestlé Research Center, Vers-Chez-Les-Blanc, CH-1000 Lausanne 26 (CH). **CROZIER, Gayle** [CA/CH]; Nestlé Research Center, Vers-Chez-Les-Blanc, CH-1000 Lausanne 26 (CH).

(74) Agent: **BECKER, KURIG, STRAUS**; Bavariastrasse 7, 80336 München (DE).

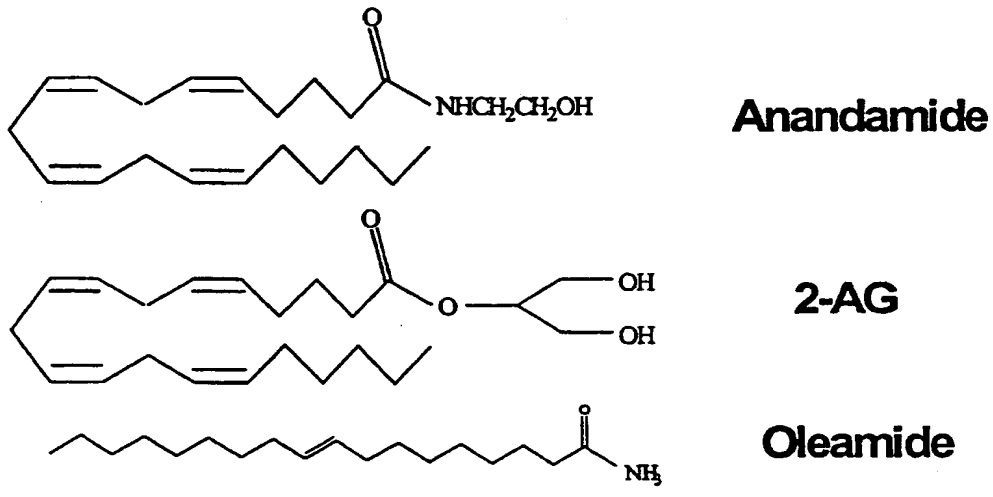
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NUTRITIONAL COMPOSITION



(57) Abstract: A nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament or nutritive product. In addition the invention includes a method of production of the composition, use of the composition in the manufacture of a nutritional composition for the treatment or prevention of a behavioural disorder; and a method of treatment or prevention of a behavioural disorder which comprises administering an effective amount of the composition. In a preferred embodiment the composition comprises a triacylglycerol having palmitate and arachidonate attached to its backbone wherein arachidonate is at the *sn*-1 and *sn*-2 positions.

WO 01/24645 A1

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Nutritional Composition

The present invention relates to a nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament or nutritional product, a method of production of the composition, use of the composition in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of a behavioural disorder; and a method of treatment or prevention of a behavioural disorder which comprises administering an effective amount of the composition.

Within the context of this specification the word "comprises" is taken to mean "includes, among other things". It is not intended to be construed as "consists of only".

Standard nomenclature for fatty acid compounds is used. For example, the number of carbon atoms and number and position of double bonds is typified by "20:4(5,8,11,14)" for arachidonic acid: the number preceding the colon is the total number of carbon atoms, the number immediately following the colon is the number of double bonds, and the numbers in parentheses are the position of the double bonds, starting from the end of the chain bearing the carboxylic acid group. In all compounds referred to in this manner, except where otherwise indicated, all double bonds are cis.

Standard nomenclature for classes of fatty acid compounds is used indicating the location of the double bond closest to the methyl end group, typified by "n-3" or "n-6": the number following the dash denotes the position of the double bond closest to the methyl end of the molecule, counting from the methyl end. Thus, arachidonic acid is in the n-6 class, as is linoleic acid (18:2(9,12)), whereas eicosapentaenoic acid (20:5(5,8,11,14,17)) is in the n-3 class. This nomenclature is equivalent to "omega or ω" nomenclature in the literature, "ω" and "n" being interchangeable.

Anandamide (also referred to as *N*-arachidonylethanolamine) is an example of an *N*-acyl ethanolamine (hereinafter referred to as NAE). Both NAEs and *N*-acyl amines (hereinafter referred to as NAAs) , an example of the latter of which is oleamide, are naturally occurring in the human body. They have been found in the hippocampus, striatum, cerebellum, spleen, heart, plasma and cerebral spinal fluid as well as in human milk.

The term "anandamide activity" is used within the context of this specification to mean an activity selected from the group which comprises an activity attributed to the drug 9-tetrahydrocannabinol (THC), as well as affects specific to anandamide and 1- and 2-monoarachidonylglycerol isomers (hereafter denoted AG), and unique from THC. It has been suggested that anandamide and AG activities are typically, but not necessarily, mediated by binding to the receptor class, known as CB1 and CB2 receptors. These anandamide activities include, but are not limited to: antinociception, catalepsy and inhibition of locomotor activity *in vivo* and displacement of 9-tetrahydrocannabinol (THC), inhibition of adenylate cyclase, inhibition of calcium channels, activation of phospholipase A_2, release of intracellular calcium *in vitro* and inhibition of twitch response *ex vivo*.

The term anandamide, as used within the context of this specification, refers to an NAE, NAA or MAG having anandamide activity (as defined above). Accepted scientific nomenclature will be used in this specification when reference is made to specific acyl moieties of an NAE, NAA or MAG.

It is well known that pharmaceutical compounds have wide application for their calming effects and they may be used in the treatment of patients suffering from conditions such as hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, convulsions, loss of appetite, nausea, cramps, diarrhoea, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, gut upsets, or spasms, poor motor control, tics, excessive stress, spasticity or

multiple sclerosis. However, a number of these compounds are not naturally occurring in nature and in view of this, patients may be reluctant to be administered them. In the light of this there is a need for the provision of new products which include naturally occurring precursors of compounds that have a nutritive or therapeutic effect, when metabolised endogenously to active compounds with anandamide activity.

Furthermore, a problem with most commercially available drugs is that they give rise to side affects such as nausea, bloating, cramping, etc. Clearly there is a need for a composition which does not give rise to these side effects.

The method of administration of a nutritive or therapeutic compound is an important consideration. Intravenous or subcutaneous administration of drugs requires expertise, and compared to oral administration it is not as safe, convenient or acceptable to the patient. In the light of these concerns it is clear that there is a need for new nutritive or therapeutic products which may be administered orally.

In addition to the problems set out above, infant formulae are generally constructed so that they resemble human milk as closely as possible, however a plurality of components in human milk are bioactive and, because of synergies among the components, the inclusion of only one or a few of them may not reproduce the bioactivity of human milk. In view of this, a problem which presently faces researchers lies in the formulation of infant formulae or weaning foods which have components that are present in human milk and which have an equivalent activity to human milk. The problem is compounded in view of the fact that not all of the components in human milk have been identified and there are variations in the concentration of components which are present, possibly due to variations of mother's diets.

A further problem which faces nutritionists lies in the field of pet nutrition. Whereas some pets are aggressive, others are excessively timid. Muzzles have been provided which fit over the heads of aggressive animals and cover their mouths. This may not be a good solution in view of the fact that a muzzle may serve to aggravate the animal. In

the light of this, there is a need for alternative solutions for calming excessively aggressive or timid pets.

US 5874459 discloses that anandamide may act as a ligand which interacts with cannabinoid receptors in the central nervous system and gut (CB1 receptors) and/or immune cells and tissues such as spleen, thymus and lymphocytes (CB2 receptors). Furthermore, this document indicates that interactions between anandamide and these two types of cannabinoid receptors have been shown to induce physiological effects. It is described that non-arachidonyl NAEs and NAAs have been shown to inhibit anandamide inactivating enzyme. This inhibition has the net effect of potentiating the effect of anandamide.

It has been suggested that a family of NAEs and NAAs as well as *sn*-1 and *sn*-2 monoarachidonyl glycerides are agonists of anandamide receptors (here anandamide receptor refers to a receptor that anandamide might bind to, including CB1, CB2, non-CB receptors) and elicit responses analogous to that elicited by anandamide. The chemical structures of NAEs and NAAs are based on fatty acids and depending on the specific fatty acids esterified they have been shown to have different activities. For example, whereas anandamide interacts with both the CB1 receptor of the central nervous system and the CB2 receptor of the immune system, palmitolyethanolamide may interact with the CB2 receptor but not the CB1 receptor and has an anti-inflammatory effect but no known neural effect.

Nature, vol 396, page 636, (1998) discloses the results of an analysis wherein NAEs and 2 arachidonoylglycerol (2-AG) were identified from foods including human, bovine and goat milk and cocoa at various stages of processing. The document suggests that anandamide (300mgkg body weight^{-1}) and 2-arachidonyl glycerol (400mgkg body weight^{-1}) have bioactivity when taken *orally* in mice, however the compounds were active only at very high concentrations relative to the concentrations normally present in foods and the results obtained show that the amounts of anandamide, 2-AG and oleamide in foods, including milk and cocoa, are several orders of magnitude below

those requ[redacted] if administered by mouth, to reach the blood and cause observable "central effects". However, the document indicates that pure doses of anandamide, 2-AG and oleamide have calming effects and effects on the immune system when *injected* into animals. Calming effects are characterised by lessened activity, decreased nociception and greater propensity for sleep.

US 568955 discloses that synthetically produced polyunsaturated fatty acid amides and their derivatives are able to mimic the effect of naturally occurring anandamides in the brain and bind to the canabinoid receptor. The compounds described exhibit physiological activity and are reported as being useful active ingredients in pharmaceutical compositions for treatment of inflammation, migraines, spasticity, glaucoma and multiple sclerosis.

Remarkably it has now been found that a composition for oral administration may be provided which includes a precursor that is metabolised endogenously to form a compound having anandamide activity. It is particularly surprising that a dietary precursor is selectively taken up by the CNS and selectively incorporated into the NAE pool to serve as a CB receptor-binding ligand. In addition, it is remarkable that a dietary precursor induces only a small change in the phospholipid acyl composition but induces a large change in the NAE composition.

The invention addresses the problems set out above.

Accordingly, in a first aspect the invention provides a nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament or nutritive product.

In a second aspect the invention provides a method of production of a nutritional or therapeutic composition for oral administration which comprises the steps of identifying, purifying or synthesising a naturally occurring precursor that is metabolised

to a compound having anandamide activity.

In a third aspect the invention provides use of a precursor which is metabolised to a compound having anandamide activity in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausia, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception.

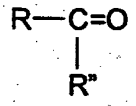
Vocalization is taken to mean disturbances in vocalisation and vocalization related to bonding behaviour, for example between an infant and mother. Such vocalisations are important in animal husbandry and in successful nurturing of the offspring by the mother in household pets. Further, such behaviours as chronic sustained crying in human infants may be treatable by oral administration of an embodiment of a composition according to the invention.

Oral administration of an embodiment of a composition according to the invention may also be used to treat or prevent inflammation in superficial mammal tissues (e.g., skin) by modulating levels of compounds with anandamide-like activity in these tissues.

In a forth aspect the invention provides a method of treatment of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausia, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering an effective amount of an embodiment of the

composition according to the invention.

Preferably the precursor that is metabolised to a compound having anandamide activity comprises a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof. More preferably it comprises a compound of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from –H, lower alkyl, -OH, NH_3, and $NHCH_2CH_2OH$, or an acid addition salt or complex thereof.

More preferably the precursor comprises a plurality of the formula X. Preferably 1-3 X molecules are esterified to a glycerol backbone, in the following sterochemical configurations: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; *sn*-3.

In an alternative embodiment the LCPUFA is a polyunsaturated fatty acid of 16-28 carbon atoms with 2-6 double bonds, having methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno- moieties.

More preferably the fatty acid is selected from the group which comprises arachidonate (20:4n-6 AA), linoleate (18:3n-6) , gamma linolenate (18:3n-6), dihomogamma-linolenate (20:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) or the Mead acid (20:3n-9).

Preferably, an embodiment of a composition according to the invention includes an inhibitor of anandamide inactivating enzyme (also known as amidase). Preferably the

inhibitor is selected from the group which comprises oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, 2-linoleylglycerol.

Preferably an embodiment of a composition according to the invention comprises a mixture of a saturated molecule in combination with an unsaturated precursor that is metabolised to a compound having anandamide activity. Preferably, the saturated molecule is palmitate or palmitoylethanolamide. Preferably the unsaturated precursor is arachidonic acid. This provides the advantage that the anandamide activity of the metabolite formed endogenously is potentiated by both inhibiting the breakdown of a metabolite having anandamide-like activity and by the saturated NAE compound binding to the CB2 receptor.

Preferably, an embodiment of a composition according to the invention comprises a mixture of a compound which reacts with a CB receptor in combination with a precursor that is metabolised to a compound having anandamide activity and an inhibitor of the amidase. This provides the advantage of synergy between the active molecules and potentiation of their effect by inhibiting the breakdown of a metabolite having anandamide-like activity.

Preferably, the precursor that is metabolised to a compound having anandamide activity is a free fatty acid, fatty acid ester of an alcohol, or a triacylglycerol. More preferably it is a triacylglycerol having an active fatty acid at the *sn*-1 and *sn*- 2 position. This provides the advantage that it leads to particularly effective CB receptor agonism. Most preferably, the triacylglycerol comprises both the active precursor compounds (eg arachidonate) and the potentiator compounds (eg palmitate). This provides the advantage of a particularly effective mixture.

Preferably, an embodiment of a composition according to the invention comprises a structured triacylglycerol prepared by the interesterification of triacylglycerols with active fatty acids so that a bioactive fatty acid is found in the *sn*-2 position of the triacylglycerol. This provides the advantage of optimising delivery of the active FA to

body tissue[redacted]rticularly the brain.

Preferably an embodiment of a composition according to the invention comprises a physiologically acceptable carrier diluent or adjuvant.

Preferably an embodiment of a composition according to the invention comprises a combination of a naturally occurring precursor that is metabolised to a compound having anandamide activity together with a typical steroidal or non-steroidal anti-inflammatory drug (NSAID). This provides the advantage that synergy occurs since the combination has the ability to diminish inflammation via different pathways.

Preferably, an embodiment of a composition according to the invention comprises a precursor of a CB1 receptor agonist (e.g. anandamide) in combination with a precursor of a CB2 receptor agonist (e.g. palmitoylethanolamide). This provides the advantage that the anti-pain effect of the metabolites is about 100 times stronger than the effect provided by the metabolites of either precursor individually.

Embodiments of the invention will now be described in further detail with reference to the accompanying drawings in which:

Figure 1 shows the chemical structure of *N*-arachidonyl ethanolamine (anandamide), 2-AG, and oleamide.

Figure 2 shows the effects of oral cannabimimetic lipids on ambulation, rearing, immobility and analgesia.

Figure 3 shows the effects of oral administration of olive oil, anandamide, 2-AG, THC and oleamide on ambulation, rearing, immobility and analgesia. Ambulation, rearing, and immobility parameters were statistically, significantly different between the treatment groups and the control group, $p<0.01$-0.05, ANOVA, Newman-Keuls; Only THC statistically, significantly increased analgesia.

Figure 4 shows the effect of olive oil, anandamide, 2-AG, THC and oleamide on body temperature. All groups were statistically, significantly different from the control group, $p<0.01$-0.05, ANOVA, Newman-Keuls.

Figure 5 shows the effect of olive oil, anandamide, 2-AG, THC and oleamide on faecal output. Only the THC group was statistically, significantly different from the control.

Figure 6 shows the changes in piglet brain *N*-acylethanolamines following dietary fatty acid modification with a scale of 0 to 250 on the axis labelled pmols/mg piglet brain lipid extract. Bars within a group of three not denoted with a letter in common are statistically significant from one another ($p<0.01$-0.05, ANOVA, Newman-Keuls). Adeq, adequate.

Figure 7 shows the changes in piglet brain *N*-acylethanolamines following dietary fatty acid modification with a scale of 0 to 70 on the axis labelled pmols/mg piglet brain lipid extract. Bars within a group of three not denoted with a letter in common are statistically significant from one another ($p<0.01$-0.05, ANOVA, Newman-Keuls). Adeq, adequate.

Piglets were fed using two different kinds of adapted infant formulations supplemented with low levels of arachidonate and docosahexaenoate (approximately the same levels as found in human breast milk) and obtained from different sources (see Table 1). The levels of NAE, MAG (monoacylglycerol) and primary amides were evaluated in their brains.

In this study piglets were fed from birth to 18 days with diets comprising embodiments of a composition according to the invention with or without 0.5% 20:4n-6 from single cell oils and 0.4% 22:6n-3 in formula, with either low (deficient) 18:2n-6(1.6%) and 18:3n-3(0.1%), or with adequate 18:2(n-6)(15.6%) and 18:3n-3(1.5%).

The diet compositions are shown in table 1.

Table 1 Formulas varied in n-3 and n-6 fatty acid content

Fatty Acid	18:2n-6 – 18:3n-3 deficient			18:2n-6 - 18:3n-3 adequate			
	No LCP	Egg+ fish Oil	Single cell oil	No LCP	Egg + fish oil	single cell oil	Sow milk
	g/100g fatty acids						
8:0	8.0	7.0	7.4	17.2	15.5	14.9	
10:0	6.7	5.9	6.5	13.5	12.6	13.0	
12:0	44.2	39.7	42.9	1.0	0.3	0.3	0.1
14:0	17.1	15.6	16.8	0.8	0.6	0.6	2.4
16:0	9.5	10.5	9.5	11.3	12.1	10.9	28.1
18:0	3.4	4.0	3.5	3.2	3.5	3.3	5.6
16:1	0.1	0.34	0.1	0.1	0.3	0.2	4.7
18:1	8.1	10.4	9.3	33.3	33.4	35.1	32.6
18:2n-6	1.6	3.8	1.9	15.6	16.0	16.4	20.4
18:3n-6	-	0.6	0.1	-	0.4	0.1	0.2
20:2n-6	-	-	-	-	-	-	0.4
20:3n-6	-	-	-	-	-	-	0.2
20:4n-6	-	0.1	0.4	-	0.1	0.4	0.7
22:4n-6	-	-	-	-	-	-	0.1
18:3n-3	0.1	0.5	0.1	1.5	1.8	1.6	2.3
20:5n-3	-	0.1	-	-	0.1	-	0.1
22:5n-3	-	-	-	-	-	-	0.6
22:6n-3	-	0.3	0.3	-	0.3	0.3	0.1

Changes in individual brain phospholipid classes that occurred after feeding were analysed.

The results showed that the addition of 20:4n-6 and 22:6n-3 to diets containing adequate levels of essential fatty acids (18:2n-6 and 18:3n-3) lead to an increase in 22:6n-3 in phosphatidyl choline; a decrease in 22:5n-6 in phosphatidyl ethanolamine; and no change in arachidonate (20:4n-6) in any of the phospholipid classes.

Thus, the small, unsubstantial increase seen in 22:6n-3 in phosphatidyl choline is consistent with the fact that the relevant diet had added 22:6n-3; however the lack of significant increase in arachidonate in any of the phospholipid classes examined indicates that added arachidonate is not incorporated into these phospholipid classes, but

rather is metabolised or inadequately transported to the brain.

The primary amides, oleamide and arachidonamide, and 18:3 NAE were not detected and are omitted from table 2, which shows the changes in levels of MAG and NAE expressed as pmols/mg lipid that occurred following feeding of the diets.

Table 2

Monacyl glycerols (MAG)

Group	C20:4n-6	C22:4n-6	C22:6n-3
Adequate	66.0	3.53	3.87
adequate + SCO	44.4	6.23	5.93
Sow fed	44.1	6.13	6.67

Table 3

***N*-acyl-ethanolamines (NAE)**

Group	C16:0	C18:0	C18:1n-9	C18:2n-6
Adequate	114.87	27.90	27.00	8.57
adequate + SCO	149.93	63.87	15.97	2.90
Sow fed	95.07	3.13	1.40	9.80

Table 4

***N*-acyl-ethanolamines (NAE)**

Group	C20:4n-6	C20:5n-3	C22:4n-6	C22:5n-3	C22:6n-3
Adequate	6.10	32.87	14.80	3.63	3.80
adequate+ SCO	23.77	172.37	23.07	33.67	36.10
Sow fed	19.97	165.63	29.30	28.00	15.77

MAG levels were not statistically significant for 20:4n-6 MAG, 22:4n-6 MAG and 22:6n-3 MAG in animals fed essential fatty acid sufficient diets (*sn*-1 and 2 isomers combined). This is an important finding because specific MAGs, such as 2-AG are

known to bind to CB receptors and have bioactivity.

In animals fed the 18:2n-6/18:3n-3 sufficient diets, supplementation with AA and DHA led to increases in 20:4n-6 NAE and 22:4n-6 NAE (22:4n-6 is the 2-carbon elongation product of AA), 22:6n-3 NAE, 20:5n-3 NAE and 22:5n-3 NAE (the latter two are retroconversion products of 22:6n-3). The levels of these NAE products were similar to that found in sow milk fed piglets. Thus, it is a remarkable feature of the invention that when sufficient essential fatty acids are provided in the diet, the supplementation of AA and DHA to levels found in breast milk, has the effect of increasing corresponding NAE products to levels found in sow milk.

The results obtained indicate that supplementation with AA and DHA to formulae having sufficient essential fatty acid had minimal effects on brain phospholipid acyl moieties. However, in striking contrast, the same level of supplementation led to a 4-fold increase in the level of 20:4n-3 NAE present, a 5.2 fold increase in 20:5n-3 NAE, and a 9.5 fold increase in 22:5n-3 and 22:6n-3 NAE.

In order to show the biological activity of the composition of the present invention on animal's behaviour the effect of dietary poly-unsaturated fatty acids with and without a CB-1 receptor antagonist on anxiolytic-like reponses in mice were tested. To this end, the ELEVATED PLUS MAZE TEST was applied (adapted after Handley and Mithani (Naunyn. Schmied. Arch. Pharmacol. 327: 1-5, 1984).

For the experiments male Rj:NMRI mice, obtained from Elevage Janvier, Le Genest-Saint-Isle France and weighing 10-11 g at delivery and 33-51 grams on day 42 were used. The mice were housed 10 per cage in wire cages with bedding and normal light cycle. They received *ad libitum* quantities of bottled distilled water and purified powdered diets (7.5 g/mouse) in ceramic cups (10/group) for 42 days. The Food was maintained at –80 °C in daily aliquots under nitrogen, thawed each afternoon before administration to mice. Uneaten food was discarded daily.

The principle of the test resides in that anxiolytic agents increase the number of entries into the open and often the closed arms of the elevated Consequently, mice should want to move and explore the spaces of the open and closed arms rather than staying still in the middle).

Mice were given the following agents intraperitoneally 60 minutes before the Plus Maze test:

Tween 80 as placebo;

the anxiolytic agent Clobazam at a non-sedative dose for test validation; or

validated amounts of AM251 (Tocris Cookson LTD., UK), a CB-1 receptor antagonist, to inhibit binding of endogenous NAEs to the CB-1 receptor.

All diets contained 90% fat-free AIN93G rodent diet in powder form (Lot 9350-5, Dyets, Inc., Bethlehem, PA), 0.4% milk fat, 1.2% palm olein, 1.9% Trisun sunflower oil, 1.5% soybean oil and 2.1-5.1% medium chain triacylglycerol oil. Parts of the medium chain triacylglycerol oil were replaced with 1.1% algal oil (providing 0.5 dietary wt.-% arachidonic acid) in diet D, 1.9% fish oil (providing 0.5 dietary wt.-% docosahexaenoic acid) in diet E, and with 1.1% algal oil and 1.9% fish oil in diets F and G. Dietary groups are summarized in the table below:

Diet Code	Diet Description	Agent given before Plus Maze Test
A	Control Diet	Tween 80, 1% distilled water solution
B	Control Diet	Clobazam, 32 mg/kg body weight
C	Control Diet	AM 251, 64 mg/kg body weight
D	Diet AA	Tween 80, 1% distilled water solution
E	Diet DHA	Tween 80, 1% distilled water solution
F	Diet AA+DHA	Tween 80, 1% distilled water solution
G	Diet AA+DHA	AM 251, 64 mg/kg body weight

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid

The body weight, weight gain and the food intake of the mice was monitored throughout the experiment. These parameters were not significantly affected by ingestion of the various diets using classical one way analysis of variance (ANOVA). This indicates that differences in the behavioral tests as found can only be attributed to the components in

the diet that were varied, namely dietary polyunsaturated fatty acids. To assess changes in the Plus Maze test, generalized Linear Models (GLM) and the *Poisson* family were used because the obtained response data are non-normally distributed counts.

Number of Entries in the Closed Arms

A vs. B: Average entries were 3.6 and 6.3, respectively, and the difference is at the limit of statistical significance (p-value = 0.053). This result establishes that the anxiolytic agent Clobazam, under the present conditions, can increase closed arm entries.

A vs. C: There was no significant difference (p-value = 0.19).

A, D, E and F: overall, the p-value is 0.06. The fitted average entries are respectively 3.6, 6.4, 6.0 and 6.8. In group D, there is one mouse with 16 entries, which is unusally high. Omitting this mouse, the p-value becomes significant (0.02) and the prediction for group

D decreases to 5.3. This result establishes that the combination of dietary AA and DHA may induce anxiolytic (Clobazam-like) effects.

F vs. G: Average entries are respectively 6.8 and 4.6, and the difference is at the limit of statistical significance (p-value = 0.11). This result indicates that the anxiolytic effects of the combination of dietary AA and DHA may be transduced via CB-1 receptor binding, i.e., via binding of PUFA-derived NAEs.

C vs. G: Average entries are respectively 2.3 and 4.6, and the difference is close to statistical significance (p-value = 0.08). This result indicates that CB-1 receptors are not the only receptors that mediate responses in the PLUS MAZE TEST, i.e., non-CB-1 receptors may partially mediate the actions of dietary PUFA and (PUFA-derived) NAEs. Additionally, the drug AM251 may not fully antagonize CB-1 receptor binding.

In summary, the results from the number of entries into the closed arms in the

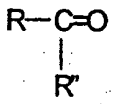
ELEVATED PLUS MAZE TEST show that dietary AA and DHA and the combination of the two, have anxiolytic-like effects that seem to be mediated via their conversion to NAEs, and these NAEs in turn bind to CB-1 receptors located in brain regions known to induce behavioral responses in the PLUS MAZE TEST, such as the hippocampus.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

Claims

1. A nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament.

2. A composition according to claim 1 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from –H, lower alkyl, -OH, NH_3, and $NHCH_2CH_2OH$, or an acid addition salt or complex thereof.

3. A composition according to claim 2 wherein the precursor comprises a molecule having a plurality of formula X.

4. A composition according to claim 2 or 3 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone, in a sterochemical configuration selected from: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; *sn*-3.

5. A composition according to any of the preceding claims, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, having a methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, or a seleno- moiety.

6. A composition according to any preceding claim wherein the precursor comprises a fatty acid selected from the group which comprises arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogamma-linolenate (20:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) or the Mead acid (20:3n-9).

7. A composition according to any preceding claim wherein the precursor comprises arachidonate (20:4n-6 AA).

8. A composition according to any preceding claim which comprises an inhibitor of an anandamide inactivating enzyme (amidase).

9. A composition according to claim 8 wherein the inhibitor is selected from the group which comprises oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, 2-linoleylglycerol.

10. A composition according to claim 8 or 9 wherein the inhibitor is palmitate or palmitoylethanolamide.

11. A composition according to any preceding claim which comprises a triacylglycerol having palmitate and arachidonate attached to its backbone wherein arachidonate is at the *sn*-1 and *sn*- 2 positions.

12. A composition according to any preceding claim which comprises a compound which reacts with a CB receptor.

13. A composition according to any preceding claim which comprises a steroidal or

non-steroidal anti-inflammatory drug (NSAID).

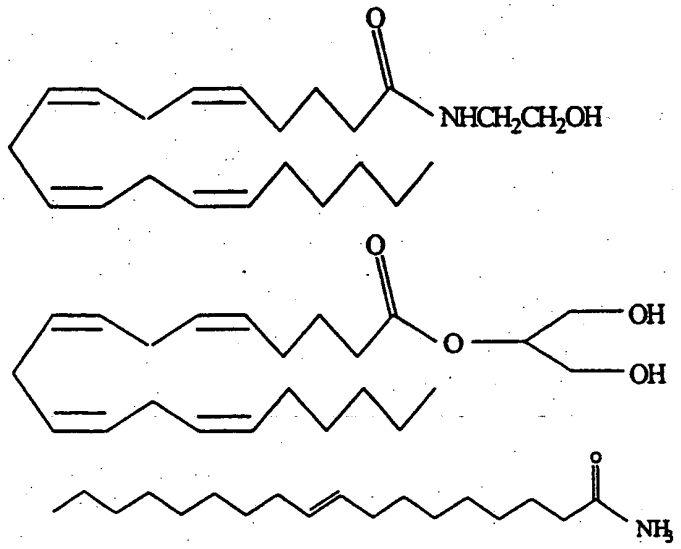
14. A composition according to any preceding claim which comprises a physiologically acceptable carrier, diluent or adjuvant.

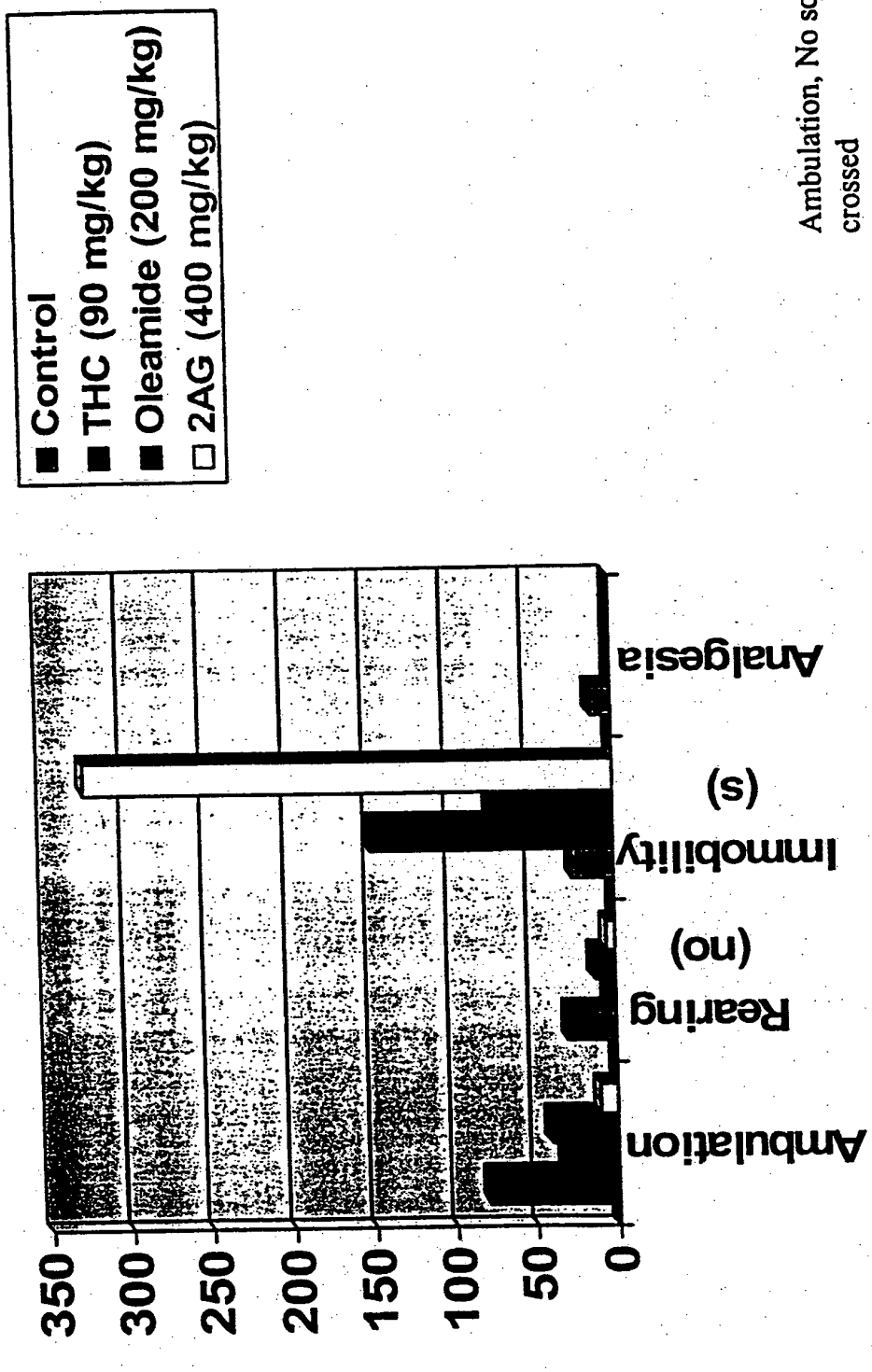
15. A method of production of a nutritional or therapeutic composition for oral administration which comprises the steps of identifying, purifying or synthesising a naturally occurring precursor that is metabolised to a compound having anandamide activity.

16. Use of a composition according to any one of claims 1 to 14 in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausia, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception.

17. A method of treatment of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausia, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering an effective amount of a composition according to any one of claims 1 to 14.

Fig. 1

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THC (90 mg/kg)
Oleamide (200 mg/kg)
2AG (400 mg/kg)
Ambulation, No squares crossed
Ambulation
Rearing (no)
Immobility (s)
Analgesia
350
300
250
200
150
100
50
0

Fig. 2

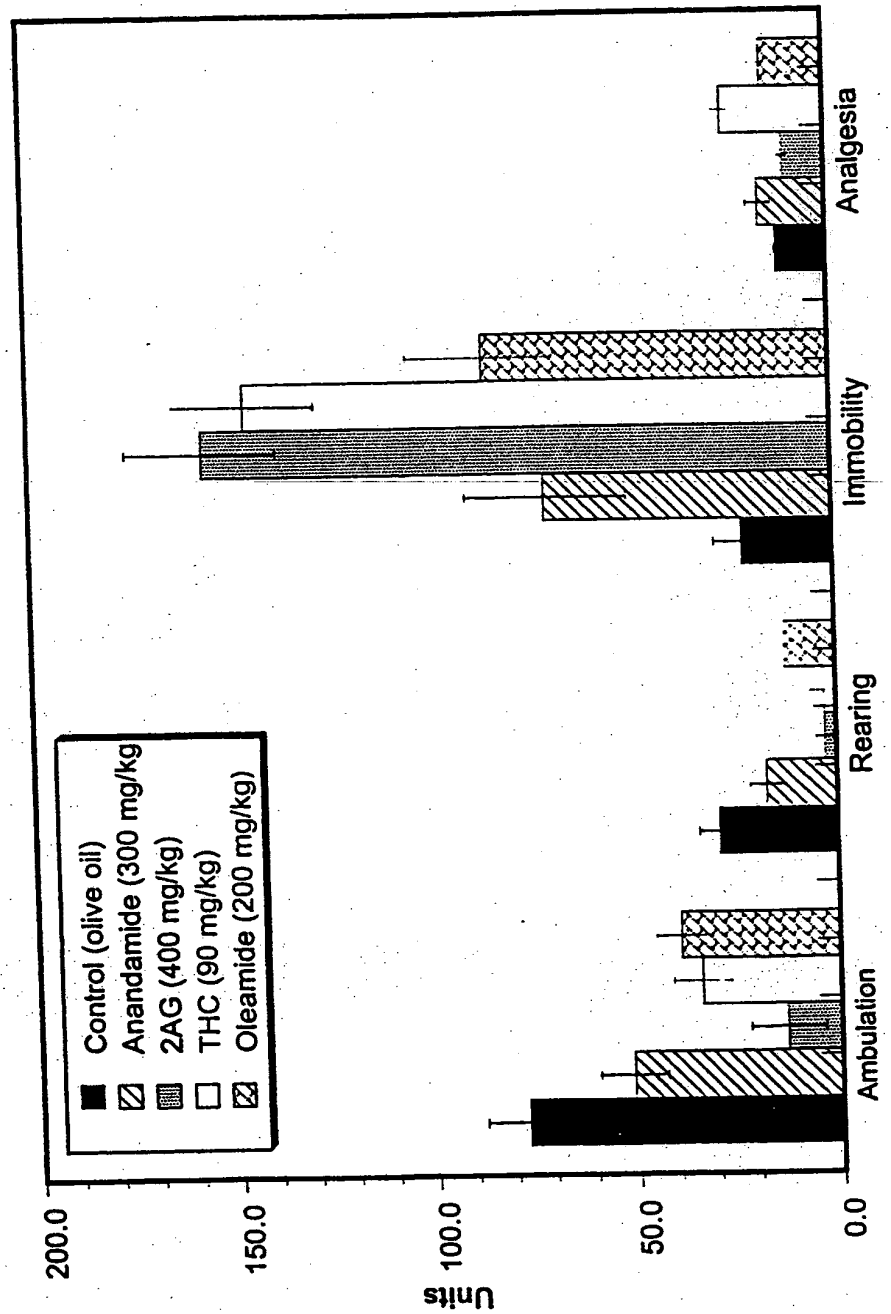
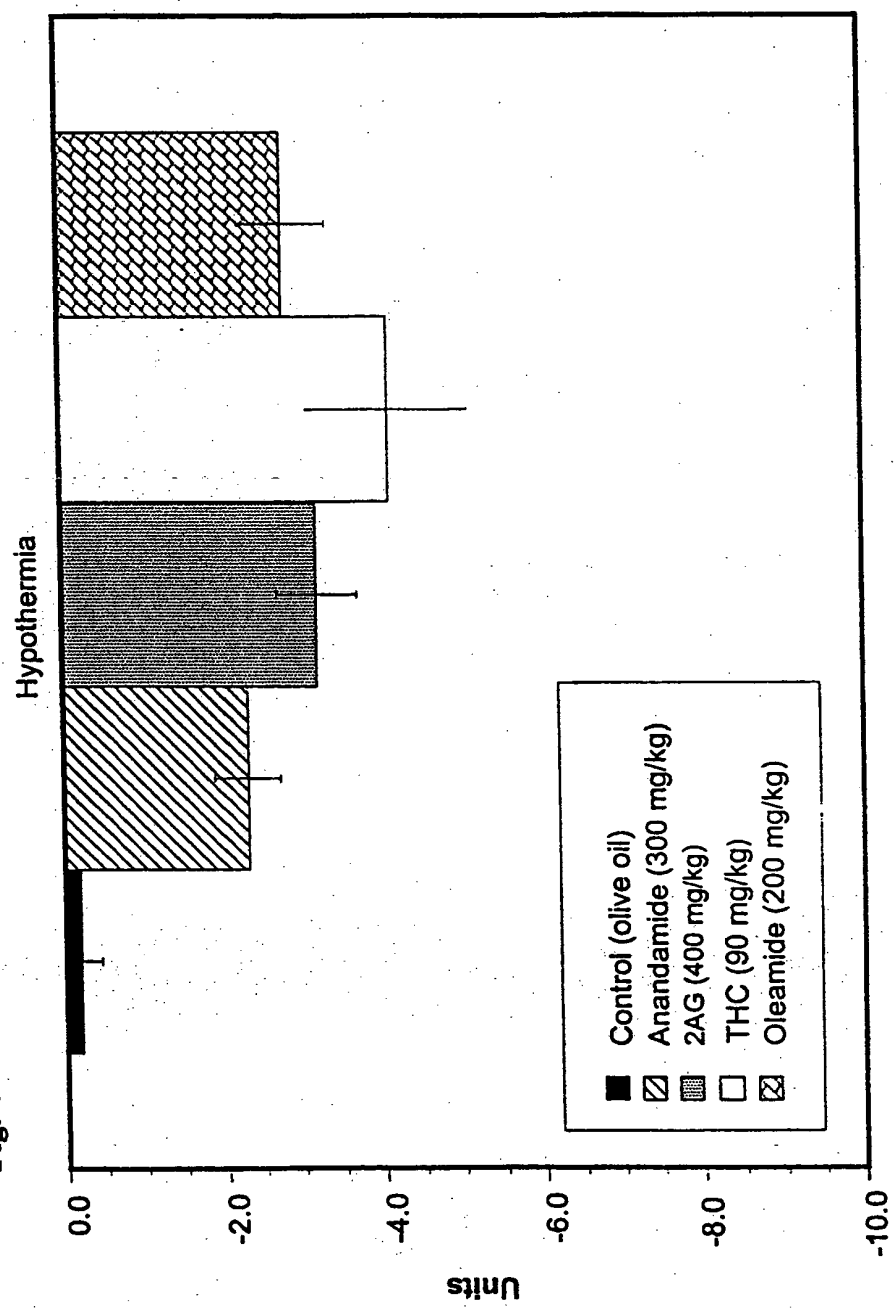


Fig. 3


Hypothermia
Units
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
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Anandamide (300 mg/kg)
2AG (400 mg/kg)
THC (90 mg/kg)
Oleamide (200 mg/kg)

Fig. 4

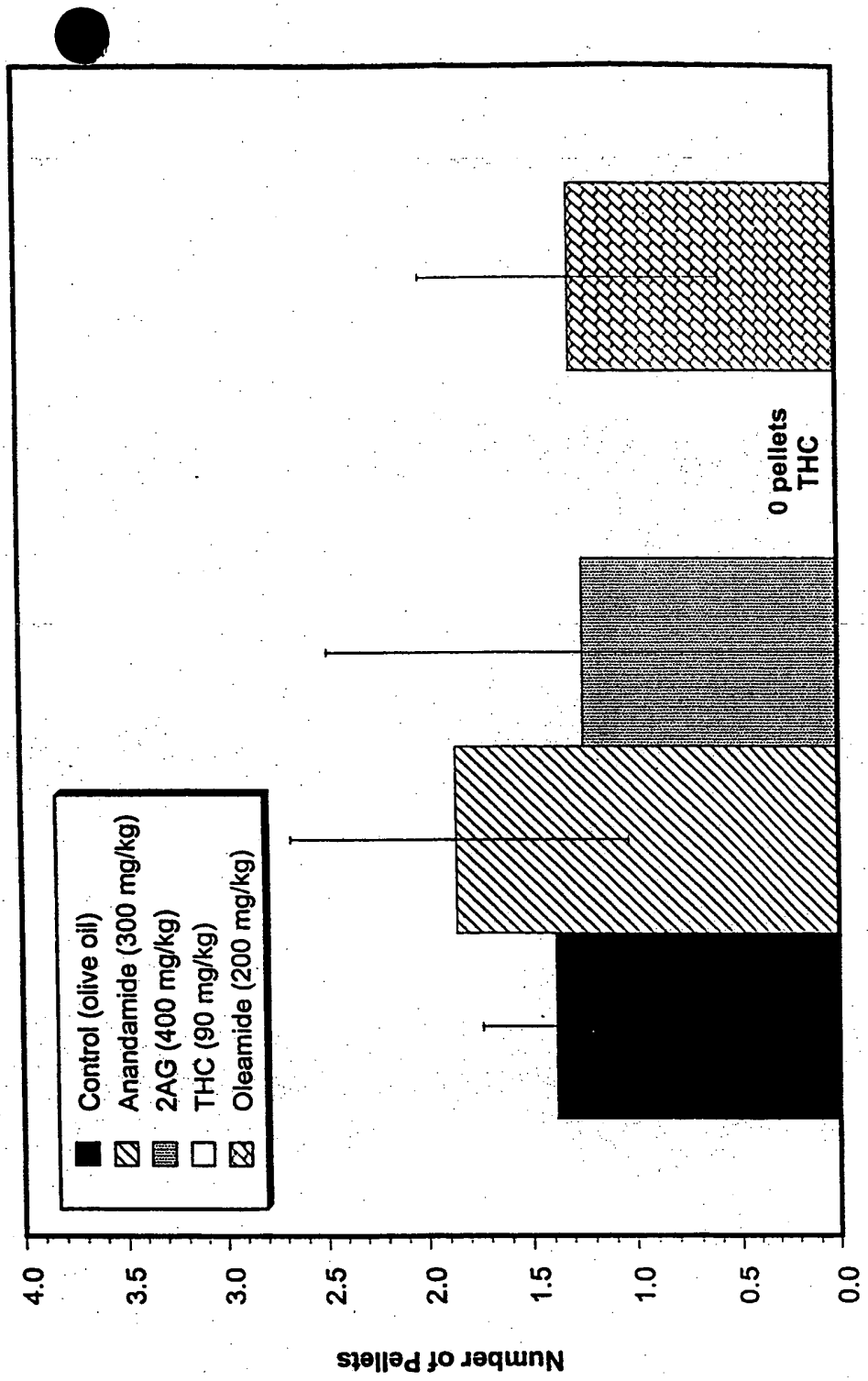
Control (olive oil)
Anandamide (300 mg/kg)
2AG (400 mg/kg)
THC (90 mg/kg)
Oleamide (200 mg/kg)
0 pellets THC
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Number of Pellets

Fig. 5

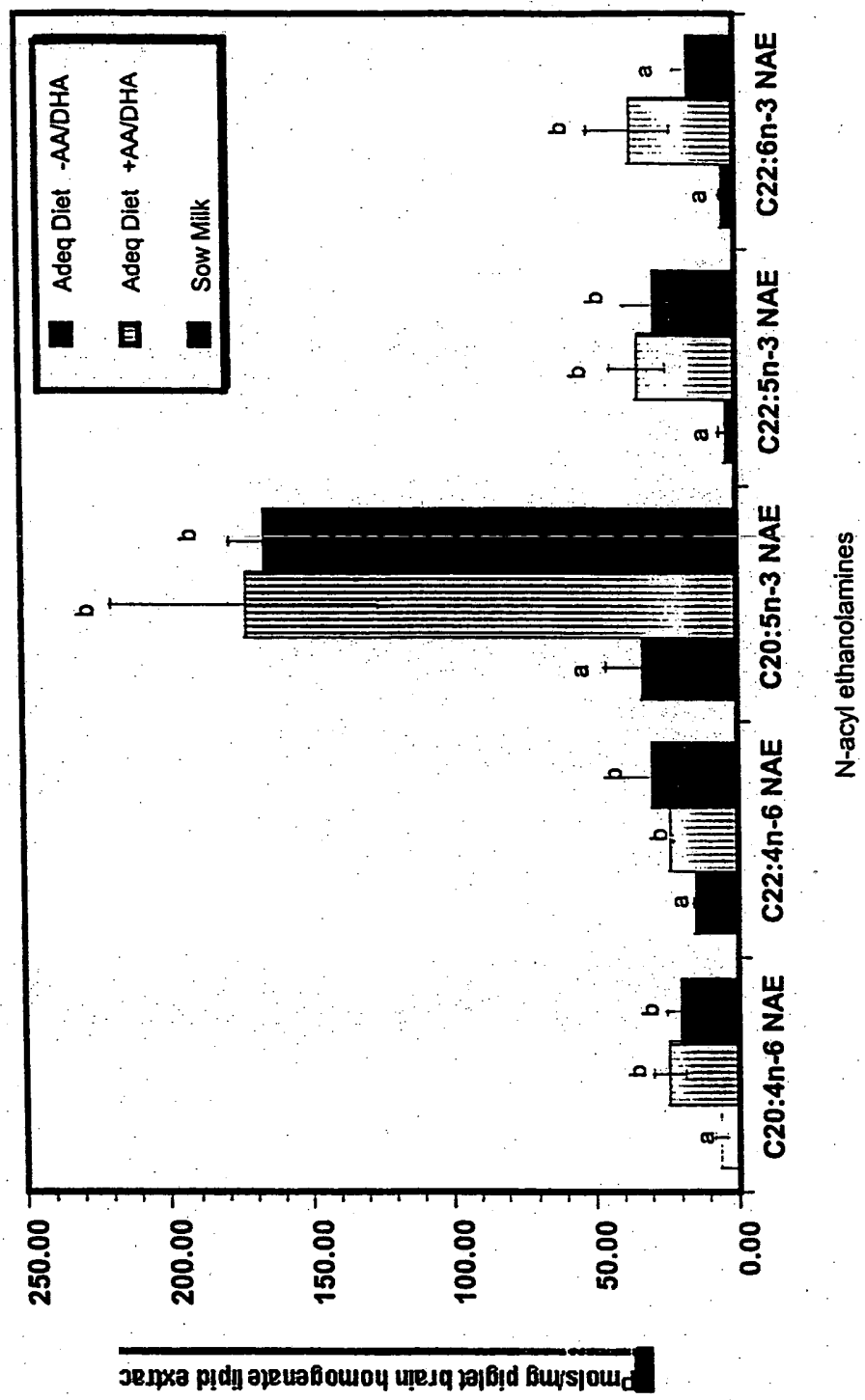
Adeq Diet -AA/DHA
Adeq Diet +AA/DHA
Sow Milk
250.00
200.00
150.00
100.00
50.00
0.00
C20:4n-6 NAE
C22:4n-6 NAE
C20:5n-3 NAE
C22:5n-3 NAE
C22:6n-3 NAE
N-acyl ethanolamines

Fig. 6

10/089658

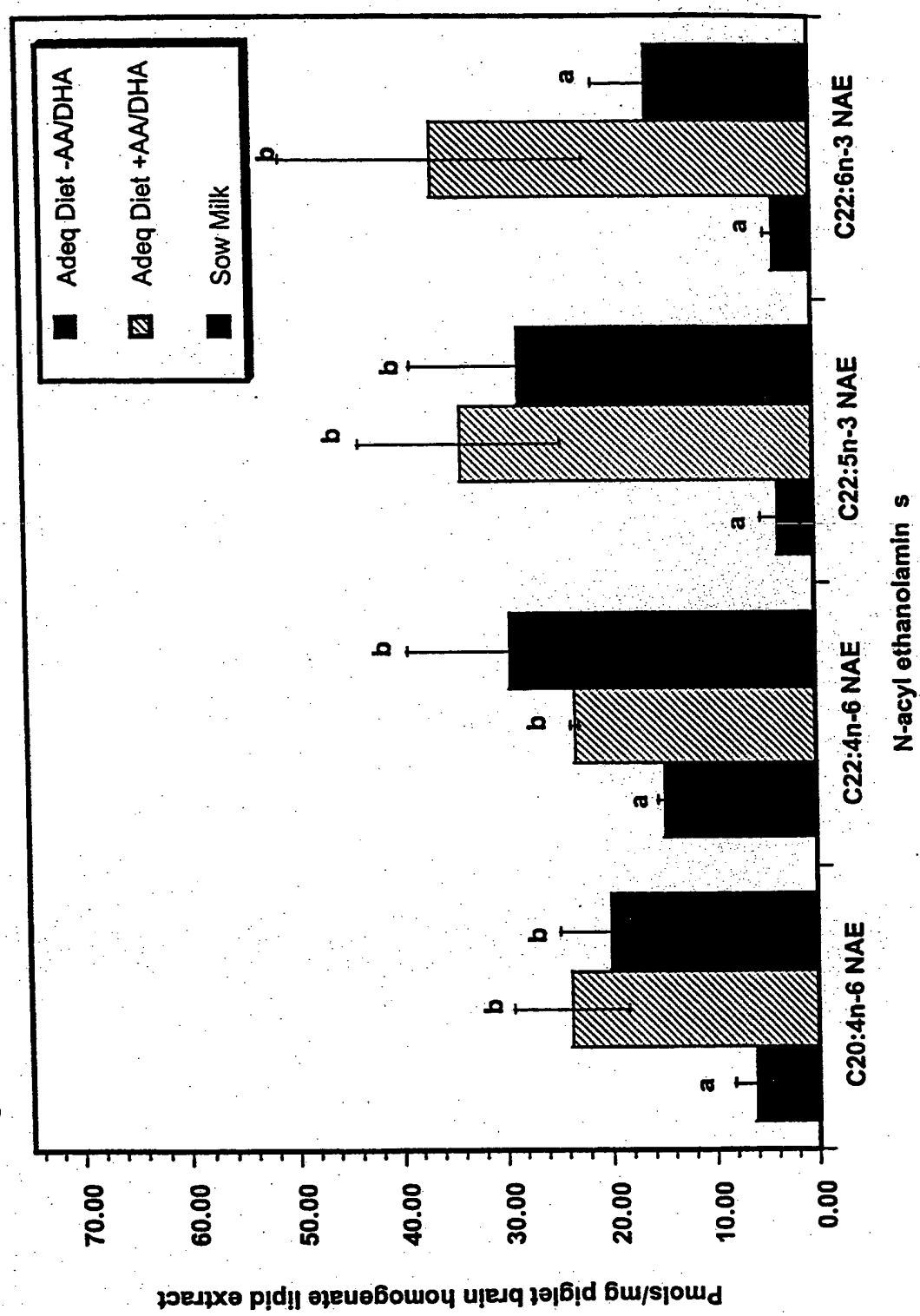

Fig. 7

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 00/08995

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/30 A61K31/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, FSTA, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40106 A (MARTEK BIOSCIENCES CORP ;KYLE DAVID J (US); LINSERT HENRY JR (US)) 19 December 1996 (1996-12-19) claims 30-78	1-4,6,7, 12,14-17
A	US 5 874 459 A (HILL WILLIAM ADAM ET AL) 23 February 1999 (1999-02-23) cited in the application the whole document	1
A	WO 94 12466 A (YISSUM RES DEV CO ;DEVANE WILLIAM A (US); MECHOULAM RAPHAEL (IL);) 9 June 1994 (1994-06-09) claims	1,8-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2001	30 01 2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Lepretre, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08995

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37200 A (SCOTIA HOLDINGS PLC ;STORDY BARBARA JACQUELINE (GB)) 28 November 1996 (1996-11-28) page 1 -page 3, paragraph 1; claims; examples	1-3,6,7, 12,14-17
X	EP 0 733 360 A (SCOTIA HOLDINGS PLC) 25 September 1996 (1996-09-25) claims; examples	1-4,6,7, 12,14-17
X	EP 0 409 559 A (EFAMOL HOLDINGS) 23 January 1991 (1991-01-23) page 5, line 5 - line 55; claims; examples	1-3,6, 14-17
X	WO 94 28913 A (MARTEK BIOSCIENCES CORP) 22 December 1994 (1994-12-22) page 6, line 18 - line 28; claims	1-4,6,7, 12,14-17
X	EP 0 490 561 A (EFAMOL HOLDINGS) 17 June 1992 (1992-06-17) claims; examples	1-3,6, 14-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/08995

Box I Observations where certain claims were found unsearchable (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/08995

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9640106	A	19-12-1996	AU	6252196 A	30-12-1996
			EP	0831805 A	01-04-1998
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			AU	5232996 A	18-07-1996
			CA	2109777 A	27-05-1994
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			DK	599576 T	25-11-1996
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		DE	69015910 D	23-02-1995
		DE	69015910 T	08-06-1995
		DK	409559 T	27-03-1995
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		JP	8511533 T	03-12-1996
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		AU	652785 B	08-09-1994
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		DK	490561 T	15-04-1996
		EP	0682878 A	22-11-1995
		ES	2084787 T	16-05-1996
		GR	3020173 T	30-09-1996
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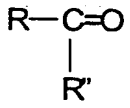
		NZ	240841 A	27-07-1997
		US	5922345 A	13-07-1999
		ZA	9109571 A	25-11-1992

Claims

1. A nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament.

2. A composition according to claim 1 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R" is selected from –H, lower alkyl, -OH, NH_3, and $NHCH_2CH_2OH$, or an acid addition salt or complex thereof.

3. A composition according to claim 2 wherein the precursor comprises a molecule having a plurality of formula X.

4. A composition according to claim 2 or 3 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone, in a sterochemical configuration selected from: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; *sn*-3.

5. A composition according to any of the preceding claims, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, having a methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, or a seleno- moiety.

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17. A method of treatment of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausia, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering an effective amount of a composition according to any one of claims 1 to 14.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08995

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/30 A61K31/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, FSTA, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40106 A (MARTEK BIOSCIENCES CORP ;KYLE DAVID J (US); LINSERT HENRY JR (US)) 19 December 1996 (1996-12-19) claims 30-78	1-4,6,7, 12,14-17
A	US 5 874 459 A (HILL WILLIAM ADAM ET AL) 23 February 1999 (1999-02-23) cited in the application the whole document	1
A	WO 94 12466 A (YISSUM RES DEV CO ;DEVANE WILLIAM A (US); MECHOULAM RAPHAEL (IL);) 9 June 1994 (1994-06-09) claims	1,8-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2001	30. 01. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lepretre, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter[illegible]pplication No
PCT/E[illegible]0/08995

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37200 A (SCOTIA HOLDINGS PLC ;STORDY BARBARA JACQUELINE (GB)) 28 November 1996 (1996-11-28) page 1 -page 3, paragraph 1; claims; examples	1-3,6,7, 12,14-17
X	EP 0 733 360 A (SCOTIA HOLDINGS PLC) 25 September 1996 (1996-09-25) claims; examples	1-4,6,7, 12,14-17
X	EP 0 409 559 A (EFAMOL HOLDINGS) 23 January 1991 (1991-01-23) page 5, line 5 - line 55; claims; examples	1-3,6, 14-17
X	WO 94 28913 A (MARTEK BIOSCIENCES CORP) 22 December 1994 (1994-12-22) page 6, line 18 - line 28; claims	1-4,6,7, 12,14-17
X	EP 0 490 561 A (EFAMOL HOLDINGS) 17 June 1992 (1992-06-17) claims; examples	1-3,6, 14-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/08995

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information [redacted] ent family members

Inter [redacted] plication No
PCT/E[redacted]/08995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9640106 A	19-12-1996	AU 6252196 A	30-12-1996
		EP 0831805 A	01-04-1998
US 5874459 A	23-02-1999	US 5688825 A	18-11-1997
		AU 3229097 A	05-01-1998
		EP 1021406 A	26-07-2000
		JP 2000511540 T	05-09-2000
		WO 9745407 A	04-12-1997
WO 9412466 A	09-06-1994	IL 103932 A	18-02-1997
		AU 5733494 A	22-06-1994
		CN 1097735 A	25-01-1995
		CZ 9501361 A	15-11-1995
		DE 69328492 D	31-05-2000
		DE 69328492 T	07-09-2000
		EP 0670826 A	13-09-1995
		ES 2145118 T	01-07-2000
		HU 73177 A	28-06-1996
		JP 8504195 T	07-05-1996
		PL 309051 A	18-09-1995
		SK 70895 A	13-09-1995
		US 5618955 A	08-04-1997
		ZA 9308947 A	02-08-1994
WO 9637200 A	28-11-1996	AU 722474 B	03-08-2000
		AU 5827796 A	11-12-1996
		CA 2195979 A	28-11-1996
		EP 0774962 A	28-05-1997
		FI 970298 A	24-01-1997
		JP 10503531 T	31-03-1998
		NO 970317 A	24-01-1997
		US 6150411 A	21-11-2000
		ZA 9604215 A	04-12-1996
EP 0733360 A	25-09-1996	AT 144706 T	15-11-1996
		AU 666782 B	22-02-1996
		AU 5183093 A	09-06-1994
		AU 5232996 A	18-07-1996
		CA 2109777 A	27-05-1994
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		DE 69305723 D	05-12-1996
		DE 69305723 T	03-04-1997
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		EP 0599576 A	01-06-1994
		ES 2093935 T	01-01-1997
		GR 3021692 T	28-02-1997
		HK 114297 A	29-08-1997
		JP 6199663 A	19-07-1994
		NO 934266 A	27-05-1994
		NZ 250265 A	24-06-1997
		RU 2123844 C	27-12-1998
		SG 47838 A	17-04-1998
		US 5516800 A	14-05-1996
		ZA 9308835 A	02-08-1994
EP 0409559 A	23-01-1991	AT 116849 T	15-01-1995
		AU 625705 B	16-07-1992
		AU 5911590 A	24-01-1991

INTERNATIONAL SEARCH REPORT

Information [redacted]ent family members

Inter [redacted]plication No
PCT/E[redacted]0/08995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0409559 A		CA 2021000 A	22-01-1991
		DE 69015910 D	23-02-1995
		DE 69015910 T	08-06-1995
		DK 409559 T	27-03-1995
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		HK 109395 A	14-07-1995
		IE 64910 B	20-09-1995
		JP 3066616 A	22-03-1991
		NZ 234528 A	24-06-1997
		ZA 9005437 A	24-04-1991
WO 9428913 A	22-12-1994	AU 693450 B	02-07-1998
		AU 6963594 A	03-01-1995
		EP 0707487 A	24-04-1996
		JP 8511533 T	03-12-1996
EP 0490561 A	17-06-1992	AT 135535 T	15-04-1996
		AU 652785 B	08-09-1994
		AU 8839791 A	11-06-1992
		CA 2056957 A	08-06-1992
		DE 69118130 D	25-04-1996
		DE 69118130 T	02-10-1996
		DK 490561 T	15-04-1996
		EP 0682878 A	22-11-1995
		ES 2084787 T	16-05-1996
		GR 3020173 T	30-09-1996
		IE 72221 B	09-04-1997
		JP 4290821 A	15-10-1992
		NZ 240841 A	27-07-1997
		US 5922345 A	13-07-1999
		ZA 9109571 A	25-11-1992

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
BECKER, KURIG, STRAUS
Bavariastrasse 7
D-80336 München
GERMANY

BECKER KURIG STRAUS
BAVARIASTRASSE 7 · 80336 MÜNCHEN
12. Feb. 2001
WV: 80.3 / LF: 30.3.01

8c

Applicant's or agent's file reference 80270/WO	Date of mailing *(day/month/year)* 30/01/2001
International application No. PCT/EP 00/08995	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant SOCIETE DES PRODUITS NESTLE S.A.	International filing date *(day/month/year)* 14/09/2000

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Emmanuel Cherqui

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rul s 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
80270/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/08995	14/09/2000	07/10/1999

Applicant

SOCIETE DES PRODUITS NESTLE S.A.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[ ] as suggested by the applicant.

[X] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/08995

Box I Observations [redacted] certain claims wer found unsearchable (Co[redacted]ion of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/30 A61K31/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, FSTA, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40106 A (MARTEK BIOSCIENCES CORP ;KYLE DAVID J (US); LINSERT HENRY JR (US)) 19 December 1996 (1996-12-19) claims 30-78 ---	1-4,6,7, 12,14-17
A	US 5 874 459 A (HILL WILLIAM ADAM ET AL) 23 February 1999 (1999-02-23) cited in the application the whole document ---	1
A	WO 94 12466 A (YISSUM RES DEV CO ;DEVANE WILLIAM A (US); MECHOULAM RAPHAEL (IL);) 9 June 1994 (1994-06-09) claims ---	1,8-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2001	30. 01. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lepretre, F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37200 A (SCOTIA HOLDINGS PLC ;STORDY BARBARA JACQUELINE (GB)) 28 November 1996 (1996-11-28) page 1 -page 3, paragraph 1; claims; examples	1-3,6,7, 12,14-17
X	EP 0 733 360 A (SCOTIA HOLDINGS PLC) 25 September 1996 (1996-09-25) claims; examples	1-4,6,7, 12,14-17
X	EP 0 409 559 A (EFAMOL HOLDINGS) 23 January 1991 (1991-01-23) page 5, line 5 - line 55; claims; examples	1-3,6, 14-17
X	WO 94 28913 A (MARTEK BIOSCIENCES CORP) 22 December 1994 (1994-12-22) page 6, line 18 - line 28; claims	1-4,6,7, 12,14-17
X	EP 0 490 561 A (EFAMOL HOLDINGS) 17 June 1992 (1992-06-17) claims; examples	1-3,6, 14-17

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9640106 A	19-12-1996	AU 6252196 A	30-12-1996
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US 5874459 A	23-02-1999	US 5688825 A	18-11-1997
		AU 3229097 A	05-01-1998
		EP 1021406 A	26-07-2000
		JP 2000511540 T	05-09-2000
		WO 9745407 A	04-12-1997
WO 9412466 A	09-06-1994	IL 103932 A	18-02-1997
		AU 5733494 A	22-06-1994
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		CZ 9501361 A	15-11-1995
		DE 69328492 D	31-05-2000
		DE 69328492 T	07-09-2000
		EP 0670826 A	13-09-1995
		ES 2145118 T	01-07-2000
		HU 73177 A	28-06-1996
		JP 8504195 T	07-05-1996
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		SK 70895 A	13-09-1995
		US 5618955 A	08-04-1997
		ZA 9308947 A	02-08-1994
WO 9637200 A	28-11-1996	AU 722474 B	03-08-2000
		AU 5827796 A	11-12-1996
		CA 2195979 A	28-11-1996
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		FI 970298 A	24-01-1997
		JP 10503531 T	31-03-1998
		NO 970317 A	24-01-1997
		US 6150411 A	21-11-2000
		ZA 9604215 A	04-12-1996
EP 0733360 A	25-09-1996	AT 144706 T	15-11-1996
		AU 666782 B	22-02-1996
		AU 5183093 A	09-06-1994
		AU 5232996 A	18-07-1996
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
80270/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 08995	14/09/2000	07/10/1999
Applicant		
SOCIETE DES PRODUITS NESTLE S.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[ ] as suggested by the applicant.

[X] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/08995

Box I Observations wher certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08995

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/30 A61K31/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, FSTA, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40106 A (MARTEK BIOSCIENCES CORP ;KYLE DAVID J (US); LINSERT HENRY JR (US)) 19 December 1996 (1996-12-19) claims 30-78 ---	1-4,6,7, 12,14-17
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	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2001	30. 01. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lepretre, F

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08995

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37200 A (SCOTIA HOLDINGS PLC ;STORDY BARBARA JACQUELINE (GB)) 28 November 1996 (1996-11-28) page 1 -page 3, paragraph 1; claims; examples	1-3,6,7, 12,14-17
X	EP 0 733 360 A (SCOTIA HOLDINGS PLC) 25 September 1996 (1996-09-25) claims; examples	1-4,6,7, 12,14-17
X	EP 0 409 559 A (EFAMOL HOLDINGS) 23 January 1991 (1991-01-23) page 5, line 5 - line 55; claims; examples	1-3,6, 14-17
X	WO 94 28913 A (MARTEK BIOSCIENCES CORP) 22 December 1994 (1994-12-22) page 6, line 18 - line 28; claims	1-4,6,7, 12,14-17
X	EP 0 490 561 A (EFAMOL HOLDINGS) 17 June 1992 (1992-06-17) claims; examples	1-3,6, 14-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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Information on patent family members

International Application No
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

1. Claims 1-66,73-77 (completely)
   Claims 70-72,78,83-83 (partially)
   Use of a composition containing oil comprising HUFA, in particular a composition containing a single cell microbial oil comprising DHA and/or ARA for treating a neurological disorder.

2. Claims 67-69
   Use of an oil enriched in DHA for lowering triglyceride content in plasma of a patient.

3. Claims 70-72,78 (partially)
   Use of a composition containing oil comprising HUFA, in particular a composition containing oil comprising DHA for treating phenylketonuria.

4. Claims 70-72,78 (partially)
   Use of a composition containing oil comprising HUFA, in particular a composition containing oil comprising DHA for treating cystic fibrosis.

5. Claims 79-82
   Use of a composition containg oil comprising HUFA for coorecting lipid imbalance in a patient.

6. Claims 83-84 (partially)
   Use of an oil enriched in DHA for treating cardiac disorders.

Groups searched: 1,2,3 and 6
Groups not searched: 4 and 5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir ational Application No PCT/US 96/08649

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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